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Computed tomographic lymphangiography of the thoracic duct by subcutaneous iohexol injection into the metatarsal region in dogs

개의 중족골 피하에 iohexl 주입을 통한 전산화단층촬영 흉관 조영술

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김 기 태

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지도교수 최 민 철

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위 원 장	윤 정 희	(인)
부위원장	최 민 철	(인)
위 원	김 민 수	(인)

Abstract

Computed tomogrpahic lymphangiography of the thoracic duct by subcutaneous iohexol injection into the metatarsal region in dogs

Kitae Kim

Veterinary Clinical Sciences (Diagnostic Imaging)

Department of Veterinary Medicine

The Graduate School

Seoul National University

The purpose of this study is to evaluate the efficacy of subcutaneous iohexol injection into the metatarsal region for thoracic duct lymphangiography in dogs and to determine the minimal effective dose. For the experimental study, iohexol injection was performed subcutaneously into the metatarsal region of 5 normal beagle dogs at three different doses (0.5, 0.75, and 1.0 ml/kg) and the regions were massaged gently. Computed tomography (CT) was performed 1, 3, 5, 7, 10, 15, and 20 minutes after iohexol injection. Subjective quality was assessed and Hounsfield unit (HU) values were measured at the different regions of interest (ROIs) (T1, T4, T8, T13, and L3). Contrast-enhanced thoracic duct was visualized in all dogs at the doses of 0.75 and 1.0 ml/kg, and in two dogs also at 0.5 ml/kg, at 3, 5, and 7 minutes. The thoracic duct was progressively more attenuated with increasing iohexol doses. The thoracic duct can be visualized by subcutaneous iohexol injection into the metatarsal region in dogs, and the minimal effective dose is 0.75 ml/kg. Subcutaneous injection of iohexol into the metatarsal region is readily applicable and can be a viable alternative to conventional thoracic duct lymphangiography.

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Keywords: CT lymphangiography, iohexol, thoracic duct, dog, metatarsal, CT subcutaneous
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Contents

Introduction

Chylothorax is the accumulation of chylous effusion in the pleural space, and it causes tachypnea, dyspnea, cough, and lethargy in dogs.[1]The therapeutic options include medical therapy and surgical intervention.[2] Surgery can potentially resolve chylothorax if the clinical signs have not improved after medical treatment or when they are intolerable.[3] Various surgical treatments have been introduced, including thoracic duct ligation,[4] cisterna chyli ablation,[5] thoracicomentalization,[6] and pericardiectomy.[7] Among these, thoracic duct ligation is the first choice,[8] and many surgeons recommend preoperative and postoperative lymphangiography for this intervention.[3,7,9,10] In a previous study, computed tomography (CT) lymphangiography was shown to allow thoracic duct identification without the superimposition of anatomic structures that may hinder its accurate evaluation in radiographic lymphangiography.[10] Moreover, the authors argued that CT lymphangiography would lead to an improvement in surgical planning and thus to increased success rates.[10]

Various methods of CT lymphangiography have been introduced: direct mesenteric lymphatic vessel injection of contrast medium during laparotomy,[11]ultrasound-guided percutaneous injection into mesenteric lymphnodes, popliteal lymph node injection,[12,13] and subcutaneous injection into the area surrounding the anus.[8,14,15] The injection into mesenteric lymphatic vessels is invasive, because it requires surgical intervention, thus increasing the total surgical time, and extreme care should be used while manipulating the dog to avoid compromising the implanted catheter.[16] Other conventional protocols, such as injection into the popliteal lymph node and mesenteric lymph node, require significant procedural experience.[8] In popliteal lymph node injection, many dogs may not have, unexpectedly, a palpable popliteal lymph node, and it may be difficult to identify one even with ultrasound guidance.[16]Subcutaneous lymphangiography is simpler than the previous protocols, and the use of the perianal region in this context was reported previously.[8] However, the metatarsal region is considered to be easier to access and to carry a lower risk of infection compared with perianal injection.[15]

Previous study suggested contrast enhancement of the peripheral lymphatic channels could be achieved by subcutaneous injection into the metatarsal region.[17] We hypothesized that central lymphatic channels could be enhanced by subcutaneous injection into the metatarsal region and the more detailed anatomic structure could be identified by the procedure. The goal of the present study was to evaluate the efficacy of subcutaneous iohexol injection into the metatarsal region for thoracic duct lymphangiography with CT in dogs and to determine the minimal effective dose of contrast material.

Materials and Methods

1. Animals

All procedures and standards of animal care were approved by the Seoul National University Institutional Animal Care and Use Committee (SNU-181227-1). Five healthy beagle dogs, weighing 7.6 – 10.0 kg (mean: 8.6 kg) were used in this study. The dogs were judged to be healthy based on physical examination and hematologic and serum chemistry analysis. Monitoring of side effects related to the injection of the contrast agent in the metatarsal region, such as lameness, skin necrosis, and irritation, was performed for 2 months.

2. Anesthetic protocol

Food was withheld for 12 – 24 hours before the CT study. All dogs were premedicated with 0.01 mg/kg acepromazine and anesthesia was induced with 2 mg/kg alfaxalone intravenously to the cephalic vein through a 22-gauge catheter and maintained with isoflurane in 100% oxygen via an endotracheal tube. The dogs were monitored for heart and respiratory rates.

3. CT metatarsal subcutaneous lymphangiography

Dogs were positioned in sternal recumbency on the CT table and the scan direction was from cranial to caudal. The hair of the metatarsal region was clipped, and the skin aseptically prepared with povidone and alcohol. Three different doses (0.5 ml/kg, 0.75 ml/kg, and 1 ml/kg) of iohexol (Omnipaque 300; GE Healthcare, Milwaukee, WI), warmed to body temperature, were administered subcutaneously for 2 minutes into the dorsal metatarsal region, using a 22-gauge catheter. After injection of the contrast medium, the injection site was gently massaged for 1 minute, then CT images were obtained using a 64-detector row CT scanner (Aquillion 64, Toshiba, Tochigi, Japan) with the following imaging conditions: tube voltage 120 kVp, tube current 150 mAs, slice thickness 0.5 mm, 0.75 sec/rotation, and 1.0 helical pitch. CT scanning was carried out 1, 3, 5, 7, 10, 15, and 20 minutes after contrast medium injection, with respiration control performed manually with the reservoir bag of the anesthetic machine. When the thoracic duct was not enhanced properly, reinjection into the opposite metatarsal region with the same dose of iohexol was performed. To rule out the influence of previously injected contrast medium, reinjection was performed after confirming that all central lymphatic ducts were not enhanced in the CT scan. CT lymphangiography was repeated at different doses (0.5 ml/kg, 0.75 ml/kg, and 1.0 ml/kg) at 2-week intervals.

4. Evaluation of CT images

CT images were reconstructed at 1 mm and further 1 mm retro-reconstruction was performed for three-dimensional (3D) reconstruction. CT images were independently viewed by two experienced observers (Kitae Kim, Kyuyong Kang), who independently and subjectively assessed the quality of the enhancement using transverse plane, multi-planar, and 3D images. During the examination, the degree of enhancement of the thoracic duct was subjectively scored as none, low, marginal, moderate, or good. If the enhanced thoracic duct was not visualized between T1 and L3, it was scored as “none.” When the length of the thoracic duct with contrast enhancement in the T1 - L3 range was less than 25%, it was scored as “low,” “marginal” if between 25 and 50%, “moderate” if between 50% and 75%, and “good” if above 75%. When both observers evaluated the contrast enhancement of thoracic duct as “good,” it was considered “well enhanced.”

The attenuation value of the thoracic duct and its branches was then measured using the transverse plane of CT images of five regions of interest (ROIs) (L3, T13, T8, T4, and T1). These ROIs were selected based on previous studies of normal anatomic features of the large lymphatic vessels in dogs.[18,19] The inner margin of the thoracic duct was traced manually, and the attenuation value was measured automatically.

5. Data analysis

All statistical analysis was performed with commercially available statistical software (IBM SPSS statistics 25.0, IBM Corp, Armonk, NY). One-way ANOVA and Tukey's test were applied to test for differences in the attenuation values of lymphatic vessels at each dose. P-values < 0.05 were considered statistically significant. Intraobserver and interobserver reproducibility were evaluated using the intraclass correlation coefficient (ICC). ICC values of 0.80 or above were considered as indicating excellent agreement.[20]

Results

Well-enhanced lymphatic vessels were identified at 3, 5, and 7 minutes in all dogs subjected to injection of 0.75 ml/kg and 1 ml/kg iohexol (Figure 1). Despite two attempts at contrast medium injection, using both metatarsal regions, well-enhanced thoracic ducts were detected only in two dogs (Dog 2, Dog 5) at the dose of 0.5 ml/kg at 3, 5, and 7 minutes (Figure 2).

With an injection dose of 1 ml/kg, peak lymphatic attenuation occurred at 5 minutes at T1 and T4 and at 3 minutes at T8, T13, and L3, while peak enhancement was observed at 5 minutes, with exception of L3, for which it was observed at 3 minutes (Figure 3). The thoracic duct was progressively more attenuated in all dogs and all measured areas with increasing dose of contrast medium at well enhanced time points (3, 5 , and 7 minutes) (Figure 3). The attenuation values were statistically different between all doses ($p < 0.05$). Agreement between the two observers regarding thoracic duct attenuation was excellent (intraobserver 1: 0.996, intraobserver 2: 0.997, interobserver: 0.994).

Moreover, the thoracic duct was well-enhanced in three dogs (Dog 1, Dog 2, and Dog 3) at 1 minute with a 1 ml/kg injection. In addition, in three dogs (Dog 2, Dog 3, and Dog 4) a well-enhanced thoracic duct with the same dose was identified also at 10 minutes, while contrast-enhanced thoracic duct disappeared at 15 minutes in all dogs. At the 0.75 ml/kg dose, a contrast-enhanced thoracic duct could not be visualized at 10 minutes in any of the dogs.

In helical CT lymphangiography, the cisterna chyli, the dilated and bipartite portion of the lymph channel, was identified at the L2 and L3 levels in all dogs. It continues cranially along the right dorsal side of the aorta through the diaphragm, then ventrally through the cranial mediastinum to the venous system where it terminates. A description of the morphological variations of the thoracic duct was possible in all dogs (Figure 4).

All dogs tolerated the injection well. No changes in respiratory or heart rate were observed after the injection. In the 2-week monitoring period for side effects after CT lymphangiography, no adverse effects were detected.

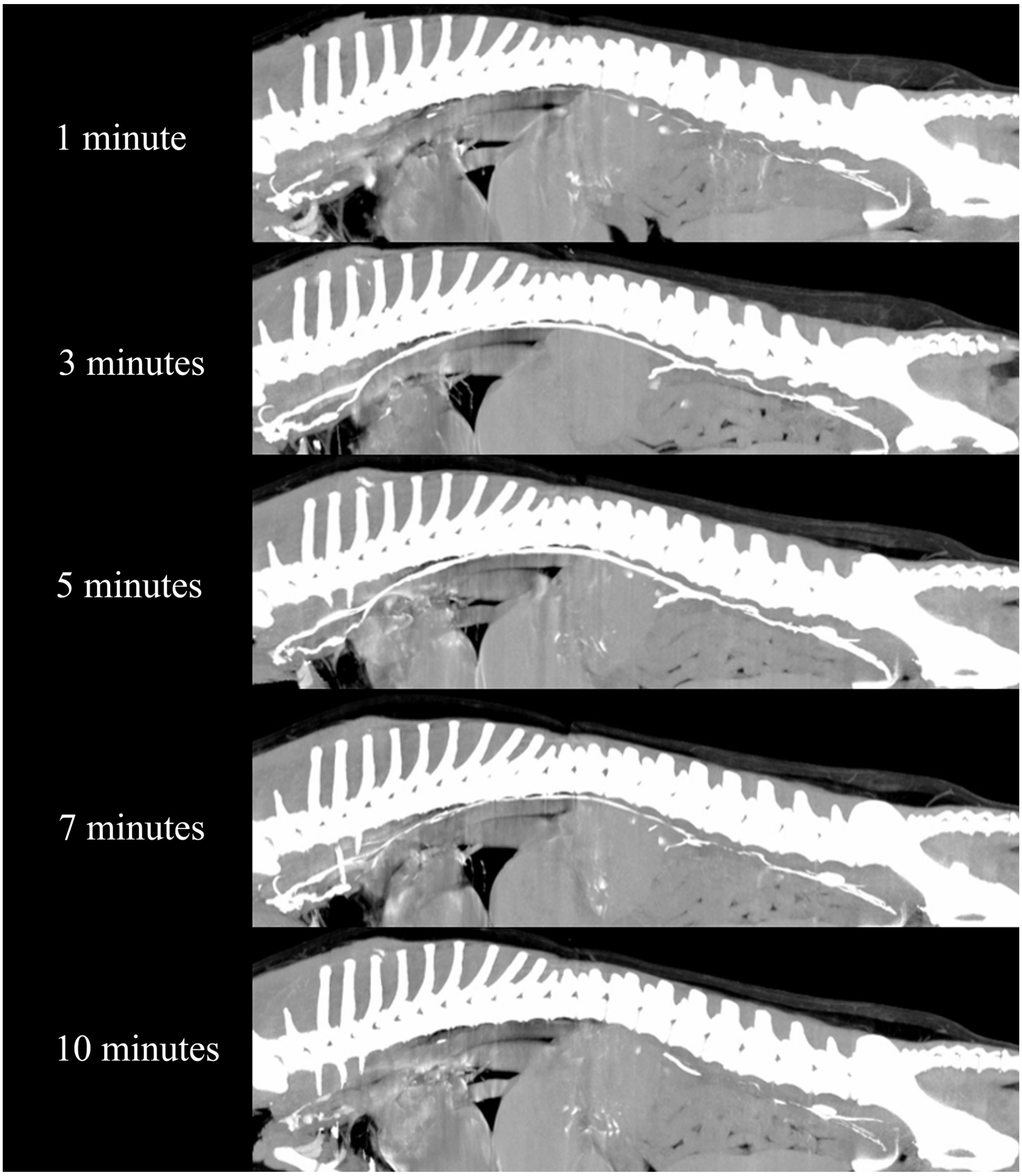

FIGURE 1. Maximum intensity projection (MIP) reconstruction CT images after CT lymphangiography with subcutaneous injection of contrast medium into the metatarsal region at the dose of 1 ml/kg. Images were obtained at 1, 3, 5, 7, and 10 minutes after injection. At 3, 5, and 7 minutes after injection, a well-enhanced thoracic duct and additional branches can be identified.

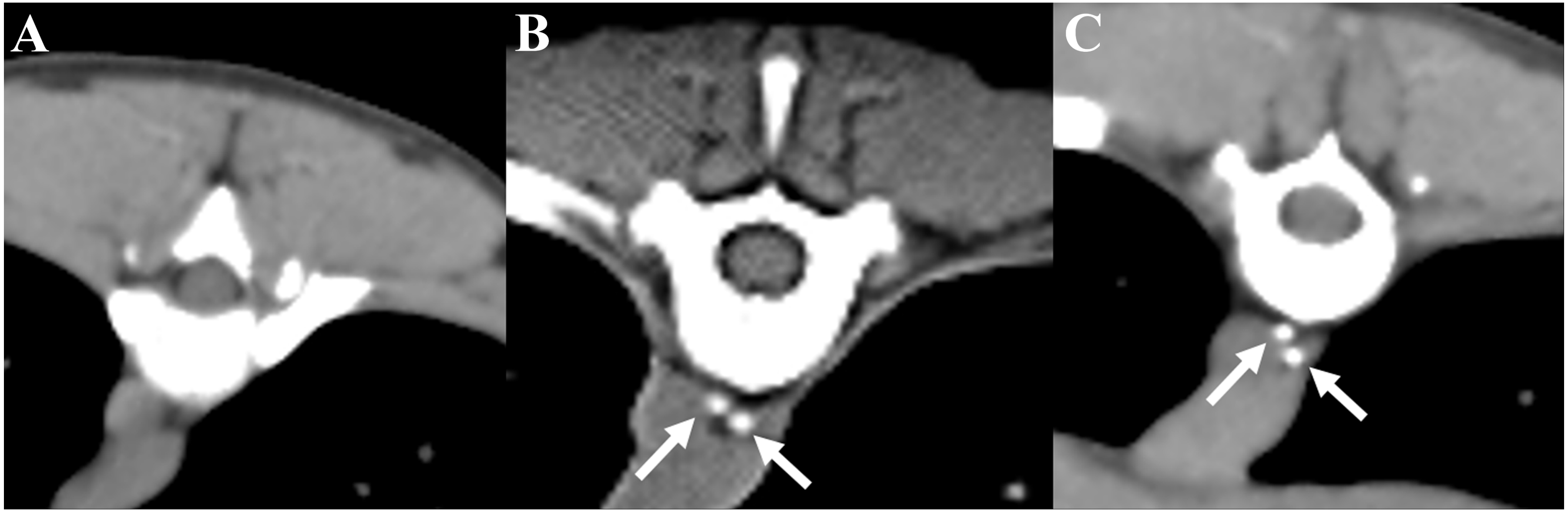

FIGURE 2 Transverse CT images at the level of T8 at the dose of 0.5 (A), 0.75 (B), 1.0 ml/kg (C), 5 minutes after injection. The thoracic duct was not enhanced after injection of 0.5 ml/kg (A). The attenuation of the left branch of the thoracic duct (arrows) was 381 HU and 614 HU (C).

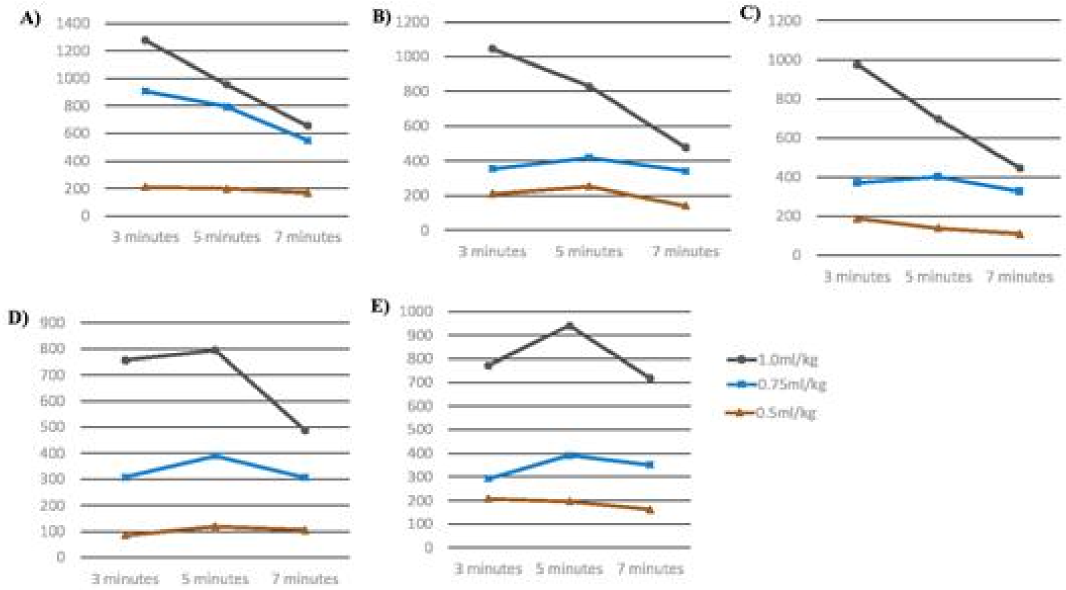

FIGURE 3 Time course (3, 5, and 7 minutes) of the mean HU value of the thoracic duct in serial transverse CT images of five ROIs after injection of three different doses of iohexol into the subcutaneous metatarsal region (A: L3 level; B: T13 level; C: T8 level; D: T4 level; E: T1 level). Statistically significant differences were observed between 0.5 ml/kg and 0.75 ml/kg and between 0.75 ml/kg and 1.0 ml/kg at all measured levels (all p-values < 0.05). At the dose of 1 ml/kg, the peak enhancement time was 3 minutes at the L3, T13 and T8 levels, and 5 minutes at the T4 and T1 levels. The HU values showed a maximum at 5 minutes, except for the T1 level at the dose of 0.75 ml/kg, where the maximum occurred at 3 minutes. At the dose of 0.5 ml/kg, a well-enhanced thoracic duct was identified only in two out of five dogs.

[redacted]

FIGURE 4 Schematic drawing of the thoracic duct in five dogs. It was possible to describe the whole thoracic duct and its branches and their variation using CT lymphangiography with subcutaneous injection of iohexol into the metatarsal region.

Discussion

In the present study, CT lymphangiography using subcutaneous iohexol injection into the metatarsal region to delineate the thoracic duct was successfully performed in all dogs at the doses of 0.75 and 1.0 ml/kg. Only two dogs (Dog 2, Dog 5) showed well enhanced thoracic ducts with a 0.5 ml/kg injection. Therefore, the minimal effective dose of iohexol to delineate the thoracic duct can be considered to be 0.75 ml/kg. A dose of 1.0 ml/kg may be required when the thoracic duct needs to be particularly evident, or when delayed CT scanning is expected, since this dose resulted in a significant higher attenuation and, in some cases, a longer enhancement time, than the 0.5 and 0.75 ml/kg doses used in all dogs.

Peak enhancement occurred earlier in the caudal than in the cranial portion of the thoracic duct after injection of 0.75 and 1 ml/kg iohexol, due to the time needed for enough iohexol to reach the cranial part of the thoracic duct. At 3 minutes, three regions (L3, T13, and T8) showed peak enhancement at the dose of 1.0 ml/kg, but only one region (L3) at the dose of 0.75 ml/kg. Presumably, more pressure was generated to fill the deep lymphatics at 1.0 ml/kg than 0.75 ml/kg, so that early detection of contrast enhancement was possible with the injection of 1.0 ml/kg.

In a previous study, thoracic duct visualization was achieved by magnetic resonance imaging (MRI) with intradermal injection of a macromolecular magnetic resonance contrast agent into the metatarsal region.[21] Another previous report suggests that subcutaneous injection of the contrast medium(gadofosveset premixed with human serum albumin) into the metatarsal region cannot result in sufficient pressure to force the agent into the deep lymphatic system, including the thoracic duct, in pigs, whereas intradermal injection of contrast medium results in sufficient interstitial pressure to fill the central lymphatics.[22] However, in the present study, a well-enhanced thoracic duct was visualized by subcutaneous injection of iohexol into the metatarsal region in dogs. In a previous study, injection of 1-2ml of water-soluble iodinated contrast medium(iopamidol) into the subcutaneous tissues overlying the pes in dogs at the level of the metatarsals was performed, and contrast-enhanced peripheral lymphatic vessels and regional lymph nodes were identified using radiography.[17] In the present study, subcutaneous injection of contrast medium into the metatarsal region resulted in sufficient pressure to force the agent into the deep lymphatic system as long as the contrast medium volume was sufficient. The maximum amount of contrast medium injected subcutaneously was determined based on the maximum recommended dose compatible with the welfare of the experimental animals(1ml/kgatonesite).[23] The lymph flow velocity is influenced by multiple factors, including posture, consciousness, respiration, and cardiac cycle.[24] Although anesthesia might interrupt the lymphatic flow, in this study the thoracic duct was well enhanced.

Thoracic duct lymphangiography is recommended as a standard procedure to observe thoracic duct branches before and after thoracic duct ligation, which is the first choice of treatment for chylothorax in small animals. To achieve successful thoracic duct ligation, the ligation site must be determined through an accurate assessment of the thoracic duct.[8,10,11]Preoperative lymphangiography can be used to assess the thoracic duct to detect hidden collateral lymphatic ducts and reduce the relapse rate. Indeed, failure to ligate all collateral branches of the thoracic duct is thought to be a common cause of operative failure in dogs.[10] Postoperative lymphangiography can confirm the successful occlusion of all thoracic duct branches so that the surgeon can be more confident that recurrent chylothorax is not due to the failure to completely occlude the thoracic duct at the time of surgery.[3] The small sample size and the analysis of only three doses of iohexol are the main limitations of the present study; however, it is likely that a larger sample size or the number of doses tests will not make a significant difference in regards to the availability of this technique and its minimum effective dose.

In conclusion, the thoracic duct can be visualized using a subcutaneous injection of iohexol into the metatarsal region at a minimum effective dose of 0.75 ml/kg. This is a simple, reliable, and less invasive method that can be used in dogs. Further studies involving more animals will be needed to confirm the safety of this technique.

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국문 초록

개의 중족골 피하에 iohexl 주입을 통한 전산화단층촬영 흉관 조영술

본 연구의 목적은 개의 흉관 조영술을 위해서 중족골 피하에 iohexol 조영제의 주입의 이용가능성을 평가하고, 그 최소 용량을 정립하고자 하는 것이다.

실험실적 연구를 위해서 세 가지의 다른 용량(0.5, 0.75, 1.0 ml/kg)의 iohexol 조영제를 다섯 마리의 정상 비글견의 중족골 피하에 주입 후 부드럽게 마사지 하였다. 전산화단층촬영을 iohexol 조영제 주입 후 1, 3, 5, 7, 10, 15, 20분 이후에 실시하였다. 주관적인 조영의 질적 평가를 진행하였으며, Hounsfield unit (HU) 값을 각각 다른 부위의 region of interest (ROIs) (T1, T4, T8, T13, and L3)에서 측정하였다.

그 결과, 조영제 주입 시간 기준으로 3, 5, 7분 후에 0.75 와 1.0 ml/kg의 용량을 주입한 모든 개체에서 조영 증강된 흉관이 확인되었으며, 0.5 ml/kg에서는 두 마리의 개체에서 확인되었다. iohexol의 용량을 증가함에 따라, 흉관의 조영의 정도가 증가하였다. 결론적으로 개에서 중족골 피하에 iohexol 주입을 통해 흉관의 영상화가 가능하였으며, 그 최소 용량은 0.75 ml/kg 였다.

중족골 피하로의 iohexol 주입은 쉽게 이용 가능하며, 기존의 흉관 조영술 시, 실행 가능한 대안으로 고려된다.

주요어: 전산화단층촬영 림프관 조영술, iohexol, 흉관, 개, 중족골, 전산화단층촬영, 피하
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